

5th October 2011

Anti-arrhythmic drug treatment
at baseline
or only after therapy?

Chris Plummer

drugs or shocks ?



goals of therapy

- ♥ prevention of SCD
 - ♥ ICD therapy
 - ♥ prevention, detection & treatment of arrhythmias with adverse prognosis
 - ♥ minimise risks of treatment
- ♥ maximise QoL
 - ♥ prevention of symptomatic arrhythmias
 - ♥ minimise of symptoms of treatment.

baseline management

- ♥ optimal pharmacological therapy
 - ♥ β -blockers
 - ♥ ACE-inhibitors
 - ♥ etc.
- ♥ appropriate device implantation
 - ♥ optimal programming
 - ♥ detection
 - ♥ ATP
 - ♥ remote monitoring.

should this patient have AAD?

- ♥ what is the risk of an arrhythmia ?
- ♥ what is the risk of ICD treatment ?
- ♥ which drug to reduce arrhythmias ?
- ♥ what is the risk of the drug(s) ?.

arrhythmia risk

risk of shocks

primary prevention

- ♥ SCD-HeFT = 5.1% pa appropriate shocks
- ♥ MADIT 2 = 12% pa appropriate shock or ATP

secondary prevention

- ♥ AVID: VF = 15.8%pa appropriate shock or ATP
- ♥ AVID: VT = 25.2%pa appropriate shock or ATP.

risk of shocks

index arrhythmia

- ♥ VT>VF (recurrence 75.5% v. 47.4% in AVID)

recent hospitalisation or shock

- ♥ time to 1st shock > 2nd (clustering SHIELD, 2005)

low EF (<25%)

- ♥ 80% shock recurrence in 1y (Freedberg, 2001)

previous “SVT” with fast ventricular rate.

therapy risk

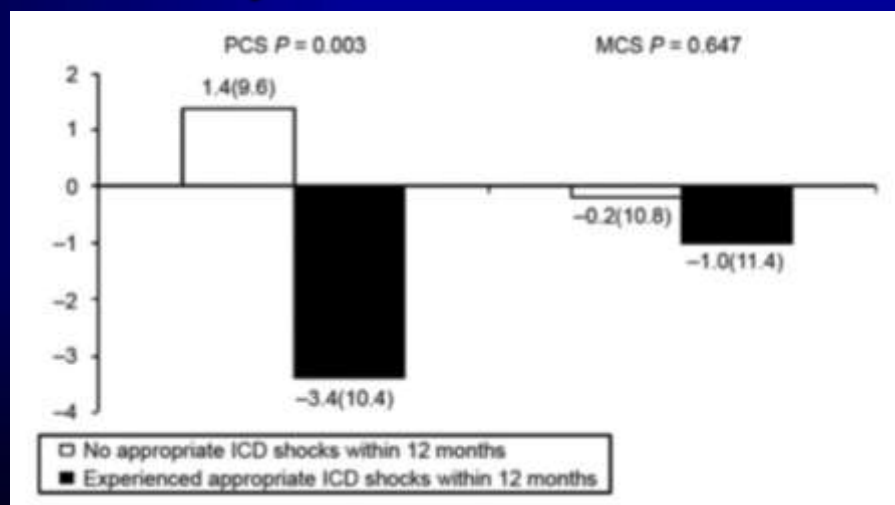
shocks - adverse effects



psychology

♥ MADIT 2

- ♥ ATP was NOT associated with any change in physical (PCS) or mental (MCS) component summary



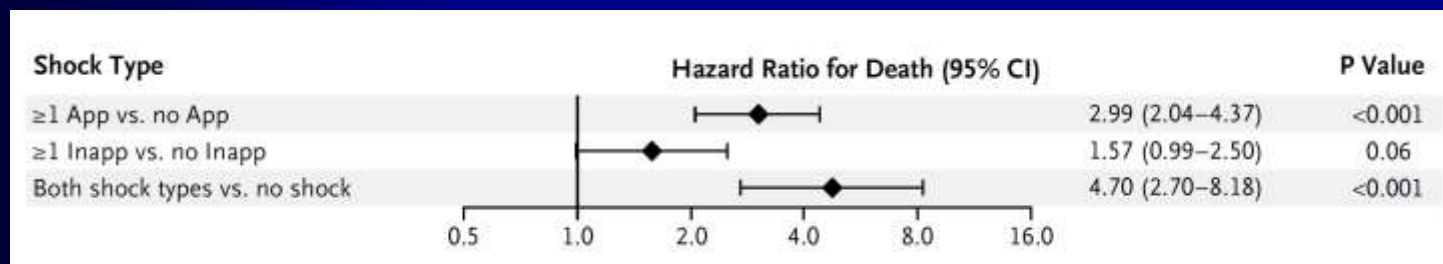
shocks - adverse effects



death

♥ SCD-HeFT

- ♥ 829 patients, 128 appropriate shock(s), 87 inappropriate shock(s), 54 both
- ♥ patients surviving >24h from shock:



shocks - adverse effects

Long-Term Clinical Course of Patients After Termination of Ventricular Tachycardia by an Implanted Defibrillator

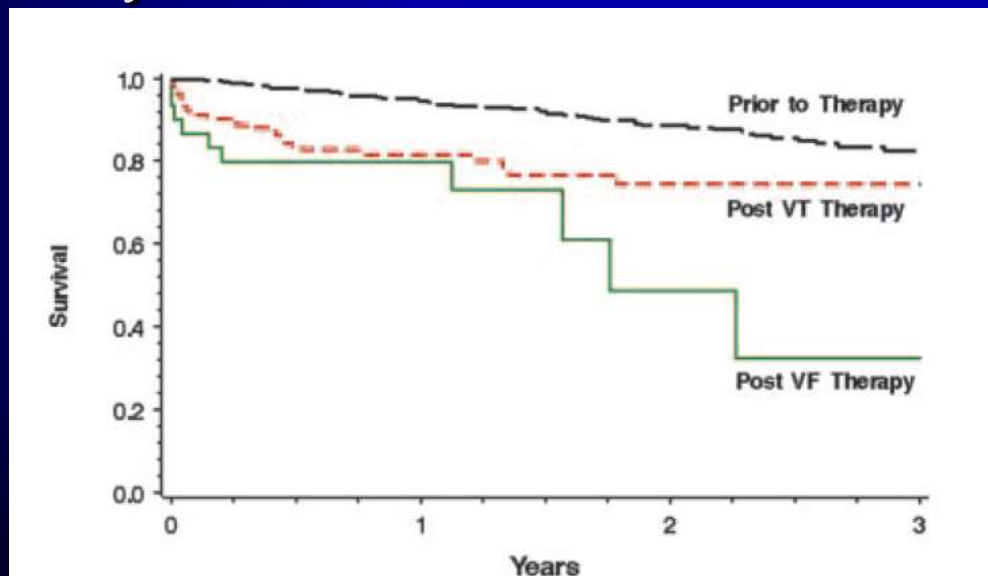
Journal of Intensive Care Medicine 1999; 14(2): 105-110

Abstract: The long-term clinical course of patients after termination of ventricular tachycardia (VT) by an implanted defibrillator (ICD) was studied. The study included 100 patients who had been treated with ICDs for VT. The mean follow-up time was 2.1 years. The study showed that the majority of patients survived long-term after ICD therapy. The study also showed that the majority of patients who received shocks survived long-term after ICD therapy. The study also showed that the majority of patients who received shocks survived long-term after ICD therapy.

death

♥ MADIT 2

- ♥ 720 patients, 169 received therapy for ventricular arrhythmia:

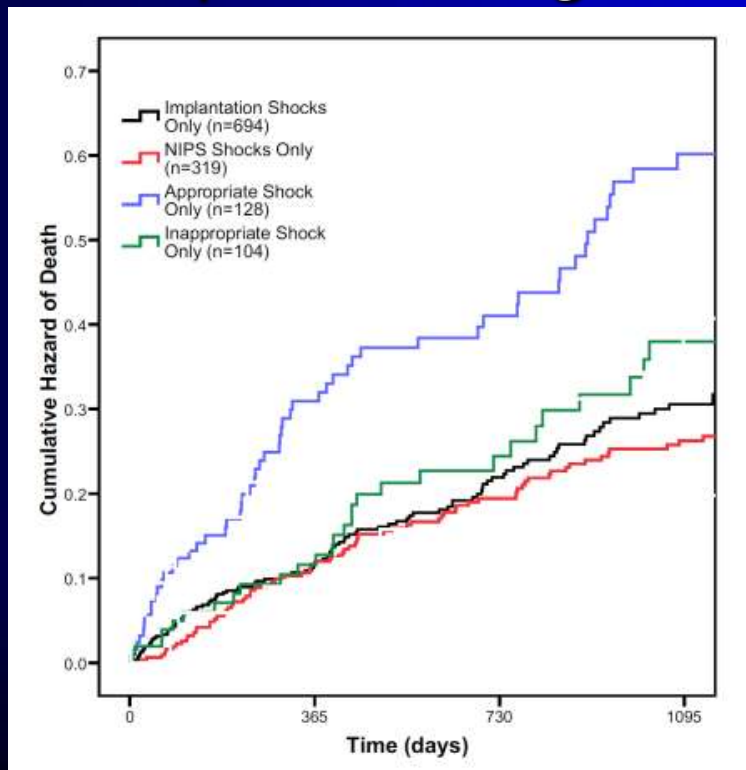


shocks - adverse effects



death

♥ retrospective single centre 10y cohort:



$p < 0.001$

*anti-arrhythmic
drugs*

potential benefits

- ♥ reduced VT
- ♥ reduced VF
- ♥ reduced AF/SVT
- ♥ increased tachycardia cycle length
 - ♥ better tolerated
 - ♥ increased ATP efficacy
- ♥ reduced shocks
 - ♥ → reduced psychological trauma
 - ♥ → reduced hospital admissions
 - ♥ → reduced battery utilisation.

harm - pharmacology

- ♥ side-effects

- ♥ cardiovascular

- ♥ bradycardia (increased RV pacing, Wolbrette 2003)
 - ♥ negative inotropic effects
 - ♥ pro-arrhythmia (tdp, AF → flutter)

- ♥ systemic

- ♥ amiodarone...

harm - device interactions

- ♥ harmful arrhythmias below detection threshold
 - ♥ class I (& amiodarone)
- ♥ increased pacing threshold
 - ♥ class IC (& amiodarone)
- ♥ increased DFT
 - ♥ inconsistent data
 - ♥ ↑ by class IB agents (Hohnloser, 1997).

class I

- ♥ no RCT in ICD patients
- ♥ CAST increased mortality
 - ♥ arrhythmic and non-arrhythmic cardiac death
- ♥ inferior to amiodarone (CASCADE)
and sotalol (ESVEM) ...

class II



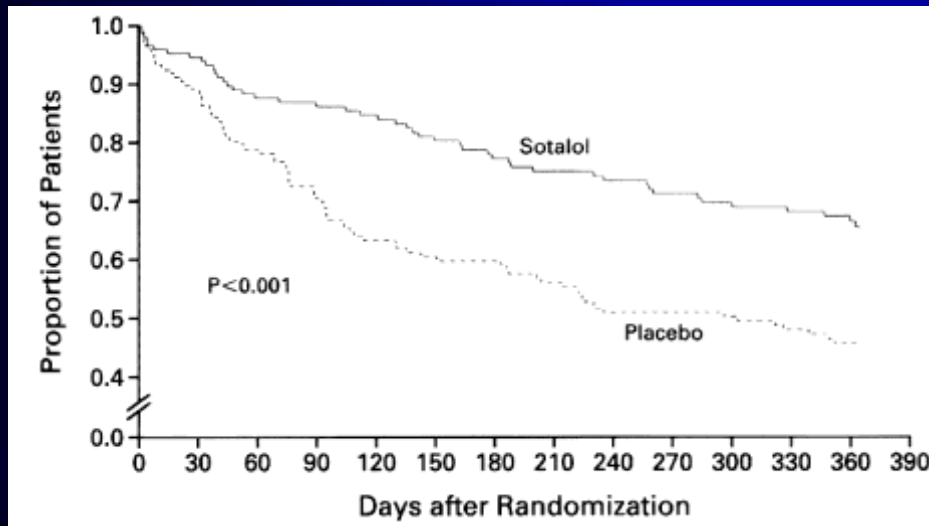
- ♥ essential in heart failure and post-MI patients
- ♥ no RCTs in ICD patients
 - ♥ CIBIS II (EF≤35%, NYHA III/IV, IHD + DCM):
 - ♥ reduced arrhythmias and SCD in patients on β-Bs:

	Placebo (n=1320)	Bisoprolol (n=1327)	Hazard ratio (95% CI)	p
Primary endpoint				
All-cause mortality	228 (17%)	156 (12%)	0.66 (0.54-0.81)	<0.0001
Secondary endpoints				
All-cause hospital admission	513 (39%)	440 (33%)	0.80 (0.71-0.91)	0.0006
All cardiovascular deaths	161 (12%)	119 (9%)	0.71 (0.56-0.90)	0.0049
Combined endpoint	463 (35)	388 (29%)	0.79 (0.69-0.90)	0.0004
Permanent treatment withdrawals	192 (15%)	194 (15%)	1.00 (0.82-1.22)	0.98
Exploratory analyses				
Sudden death	83 (6%)	48 (4%)	0.56 (0.39-0.80)	0.0011
Pump failure	47 (4%)	36 (3%)	0.74 (0.48-1.14)	0.17
Myocardial infarction	8 (1%)	7 (1%)	0.85 (0.31-2.34)	0.75
Other cardiovascular	23 (2%)	28 (2%)	1.17 (0.67-2.03)	0.58
Non-cardiovascular deaths	18 (1%)	14 (1%)	0.75 (0.37-1.50)	0.41
Unknown cause of death	49 (4%)	23 (2%)	0.45 (0.27-0.74)	0.0012
Hospital admission for worsening heart failure	232 (18%)	159 (12%)	0.64 (0.53-0.79)	0.0001

class III

sotalol

- ♥ β -blocker \pm class III
- ♥ sotalol (160-320mg od) v placebo (Pacifico, 1999)
 - ♥ 12-month follow-up
 - ♥ death or first shock:



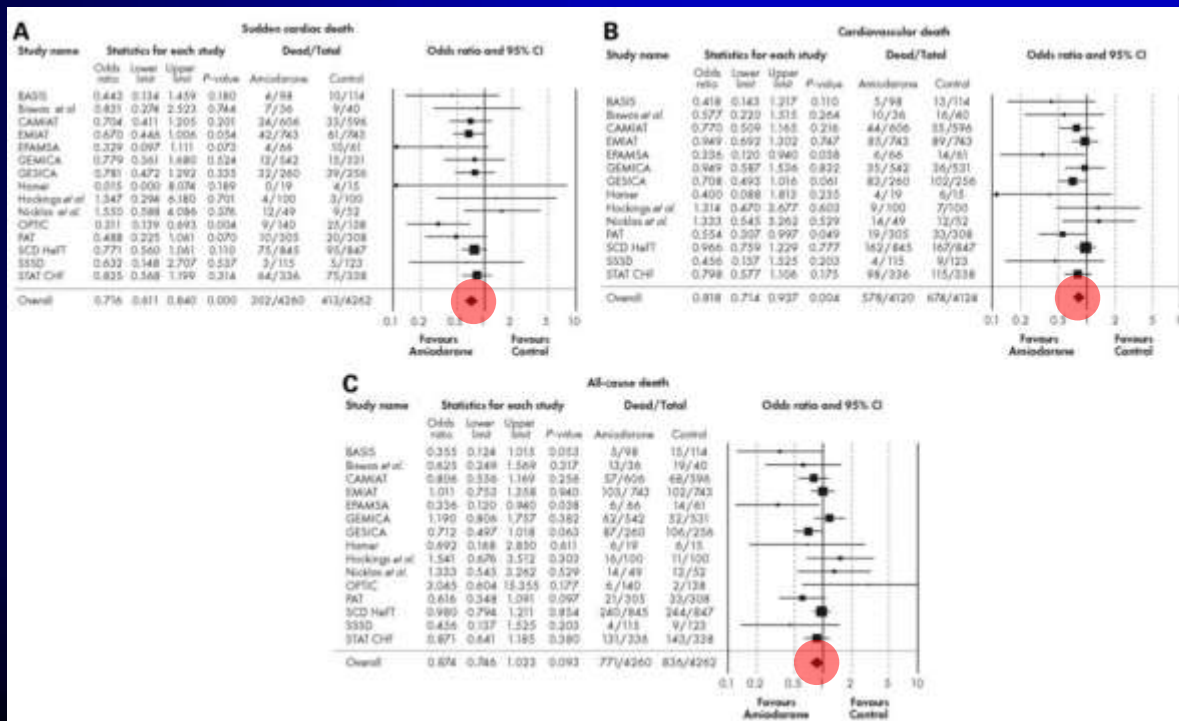
DRUG*	PLACEBO		SOTALOL	
	AT START OF TREATMENT (N=151)†	AT END OF TREATMENT (N=143)‡	AT START OF TREATMENT (N=151)†	AT END OF TREATMENT (N=142)‡
	percentage of patients			
Beta-blocker	28	37	27	23§
Calcium-channel blocker	21	27	19	23
Digoxin	38	44	35	37
Diuretics	39	52	38	48
ACE inhibitors	54	69	64	71
Digoxin, diuretic, and ACE inhibitor	19	27	15	19
Hypolipidemic agent	22	36	27	38

class III

amiodarone

♥ class I-IV

♥ meta-analysis 15 trials in patients without ICD:

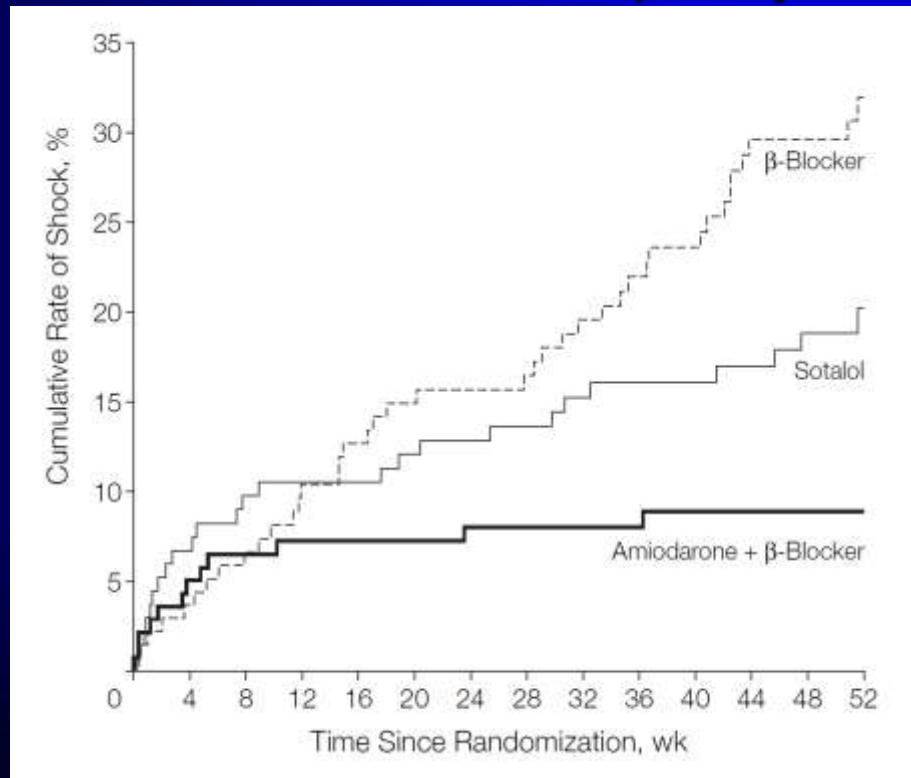


class III



amiodarone v sotalol v BB

♥ RCT blinded 412 ICD pts 1y:



$p = 0.055$

$p < 0.001$

class III - toxicity

amiodarone

Adverse reaction	Amiodarone (%)	Control (%)	Random effects odds ratio (95% CI)	P-value	Number needed to harm (95% CI)	P-value for heterogeneity
Pulmonary toxicity	82/2787 (2.9)	41/2777 (1.5)	1.97 (1.27–3.04)	0.002	69 (45–144)	0.383
Thyroid toxicity	134/3732 (3.6)	15/3724 (0.4)	5.68 (2.94–10.98)	<0.001	32 (26–39)	0.254
Hepatic toxicity	35/1889 (1.85)	16/2276 (0.7)	2.10 (1.15–3.82)	0.015	87 (54–222)	0.767
Brady-arrhythmia	90/3245 (2.8)	45/2938 (1.5)	1.78 (1.16–2.72)	0.008	81 (51–191)	0.368

- ♥ 6 pulmonary deaths ($6/8522 = <0.001\%$)
- ♥ cancer deaths ($13/1609 = 0.7\%$ v $4/1597 = 0.2\%$)
- ♥ 31.6% discontinued amiodarone
- ♥ 21.1% discontinued placebo.

class III – other agents

dofetilide

- ♥ no RCT in ICD patients
 - ♥ death or arrhythmia - similar efficacy to sotalol

azimilide

- ♥ 57% RRR for shocks at 1y, 1.2% tdp
- ♥ no UK licence

dronedronone

- ♥ no VT data, excess mortality in heart failure

celivarone

- ♥ 3 phase 2 trials & on-going trials...

VT ablation

SMASH-VT

- ♥ 128pts VT/VF, no AAD, substrate ablation
- ♥ ICD shocks reduced 31% to 9% over 22.5 months
- ♥ 5% complications (no mortality at 30d)

VTACH

- ♥ 107 pts, stable VT, substrate ablation
- ♥ ICD therapy reduced 3%pa to 0.2%pa
- ♥ 3.8% complications (no mortality at 30d)

draft HR-UK document.

conclusions

conclusions

baseline therapy

- ♥ revascularisation when indicated
- ♥ drugs for all!
 - ♥ β -blockers, ACEi, anti-platelet agents etc.
- ♥ optimal ATP for all!
 - ♥ avoid shocks

amiodarone

- ♥ after shock(s) or frequent ATP

ablation

- ♥ amiodarone ineffective or not tolerated.

conclusions

ICD implantation
(revascularisation, OPT & ATP)

shock(s) or frequent ATP

reprogramme ATP
add amiodarone
200mg od for 1y

shock(s) or frequent ATP

VT ablation

individualisation

- ♥ already on amiodarone ?
- ♥ psychological state ?
- ♥ patient preference ?
- ♥ effectiveness / harm of amiodarone ?
- ♥ previous storm ?
- ♥ risk of arrhythmia ?
- ♥ SVT ablation
- ♥ when nothing works ?!

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